Using single-operator cholangioscopy for endoscopic evaluation of indeterminate biliary strictures: results from a large multinational registry

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ABSTRACT

Background Peroral cholangioscopy (POCS) of indeterminate biliary strictures aims to achieve a diagnosis through visual examination and/or by obtaining targeted biopsies under direct visualization. In this large, prospective, multinational, real-life experience of POCS-guided evaluation of indeterminate biliary strictures, we evaluated the performance of POCS in this difficult-to-manage patient population.

Methods This prospective registry enrolled patients, with indeterminate biliary strictures across 20 centers in Asia, the Middle East, and Africa. The primary end points were the ability to visualize the lesion, obtain histological sampling when intended, and an assessment of the diagnostic accuracy of POCS for malignant strictures. Patients were followed for 6 months after POCS or until a definitive malignant diagnosis was made, whichever occurred first.

Results 289 patients underwent 290 POCS procedures with intent to biopsy in 182 cases. The stricture/filling defect was successfully visualized in 286/290 (98.6 %), providing a visual diagnostic impression in 253/290 (87.2 %) and obtaining adequate biopsies in 169/182 (92.9 %). Procedure-related adverse events occurred in 5/289 patients (1.7 %). POCS influenced patient management principally by elucidating filling defects or the causes of bile duct stricture or dilation. The visual impression of malignancy showed 86.7 % sensitivity, 71.2 % specificity, 65.8 % positive and 89.4 % negative

predictive value, and 77.2 % overall accuracy compared with final diagnosis. Histological POCS-guided samples showed 75.3 % sensitivity, 100 % specificity, 100 % positive and 77.1 % negative predictive value, and 86.5 % overall accuracy.

Conclusion In this large, real-life, prospective series, POCS was demonstrated to be an effective and safe intervention guiding the management of patients with indeterminate biliary strictures.

Introduction

Endoscopic retrograde cholangiopancreatography (ERCP) has been used as a primary diagnostic modality in the diagnosis of biliary pathology, but its role has been superseded by other noninvasive imaging procedures. However, ERCP remains an indispensable tool for obtaining tissue/cytological samples from the biliary system in the evaluation of strictures. The diagnostic performance of fluoroscopically guided transpapillary biopsies and brush cytology is suboptimal. Direct intraductal visualization of lesions and strictures of the biliary system has been achieved using a number of different instruments and techniques, each of which have benefits and limitations [1 – 3].

The SpyGlass Direct Visualization System (SpyGlass DVS; Boston Scientific, Marlborough, Massachusetts, USA) was developed as a single-operator catheter-based cholangiopancreatoscope and was first described in a preclinical study in 2007 [4]. Also in 2007, a study describing its use in 35 patients was reported by the same author [5], with its utility in obtaining samples for histological evaluation, as well as providing targeted therapy for biliary stone disease, being demonstrated. The largest prospective, multicenter, consecutive series on peroral cholangioscopy (POCS) using the SpyGlass system included 297 cases in the USA and Europe, and was published in 2011 [6]. Biliary strictures and biliary stone disease were the indications for POCS in that cohort. Since then a prospective, multicenter study was completed in the Asia, Middle East, and Africa (AMEA) regions and included 522 patients who underwent POCS for various indications, including biliary stone disease, as well as indeterminate biliary strictures. The outcomes of a subcohort of this study with difficult biliary stone disease were recently published [7].

The aim of the current study was to evaluate the performance of POCS using the SpyGlass DVS throughout the AMEA regions for patients with indeterminate biliary strictures (289 patients) in a real-life clinical setting.

Methods

Study design, study conduct, and patient population

The SpyGlass AMEA Registry was a prospective, observational, open-label, multicenter post-market study conducted at 20 sites in the AMEA region (NCT02281019 at http://www.clinicaltrials.gov; and CTRI/2014/11/005173 at http://ctri.nic.in/Clinicaltrials/login.php) after clearance or approval of the SpyGlass system in all participating countries. The centers that participated in the registry were tertiary care centers with relevant experience in the use of POCS. As per the study protocol, participating centers were required to have completed at least 10 SpyGlass procedures prior to enrolling patients undergoing SpyGlass into the SpyGlass AMEA Registry. There was no central committee monitoring data collection and image quality in this study.

Boston Scientific Corporation sponsored and funded the study. A statistician (M.J.R.) who is a full-time employee of Boston Scientific Corporation performed the data management and statistical analysis. Review and input to the analysis of the study data was provided by two Boston Scientific employees (J. P. and M.J.R.) and by all participating physicians at 11 Investigator Meetings between 2014 and 2017.

Consecutive patients with a definite or possible indication for POCS during an ERCP procedure were enrolled. Patients were stratified by their indication for POCS: biliary stone disease or indeterminate biliary strictures. The POCS evaluation of indeterminate biliary strictures is presented in this report. The inclusion criteria were patients who were: 18 years of age or older, willing and able to provide written informed consent to participate in the study, and willing and able to comply with the study procedures. Patients requiring anticoagulation therapy that could not be safely stopped at least 7 days prior to the procedure were excluded. In four patients, stones were found during their procedure for indeterminate biliary stricture. Data for these four patients were included in both the current study and a previous SpyGlass AMEA registry study of cholangioscopy-guided lithotripsy for difficult bile duct stone clearance [7].

Data were collected through a web-based system that was password protected with an electronic trail of any data entry or change. Baseline data collected included: patient demographics (age, sex); history of chronic pancreatitis, liver cirrhosis, cholecystectomy, living-donor liver transplantation, previous ERCP; as well as the indication for cholangioscopy (indeterminate strictures or undefined filling defects). Any episode of cholangitis or acute pancreatitis occurring within the 4 weeks preceding cholangioscopy was also recorded. Data related to the cholangioscopy included: the procedure setting (outpatient vs. inpatient); administration of prophylactic antibiotics; and the need for a sphincterotomy or extension of an existing sphincterotomy to be performed to facilitate either the insertion of the SpyGlass catheter or any other intervention. Recorded findings on cholangioscopy included: the location of the dominant lesion/stricture; the quality of the SpyGlass image; whether the target lesion/stricture could be adequately visualized; a description of the lesion/stricture; whether a visual impression of malignancy could be made; and the number and adequacy of the biopsies if obtained. The severity of adverse events and their outcomes were also recorded.

All centers obtained approval from their respective local ethics committees and all patients provided signed informed consent before the procedure. The study sponsor had read-only rights to the data and could not make any data entries or data changes. Safety oversight consisted of all serious adverse events being regularly tallied and their incidence being compared with values in the literature.

The procedure was deemed unsuccessful when the stricture/lesion was not visualized, a visual impression was not provided, or the SpyBite biopsy was not adequate for assessment.

Cholangioscopy procedure and sample processing

Two systems were used in the study cohort: the SpyGlass Legacy system and the more recent SpyGlass DS digital system (Boston Scientific Corporation). POCS-guided biopsies were taken using a dedicated biopsy forceps, the SpyBite forceps (Boston Scientific Corporation), which is designed to pass through the channel of the POCS catheter. The administration of prophylactic antibiotics was determined by local standards of practice within each institution and/or at the discretion of the endoscopist. In patients where a previous sphincterotomy had not been performed or had been performed but was inadequate to facilitate biliary cannulation with the SpyGlass system, a sphincterotomy was either performed or extended, respectively. The processing and reporting of biopsies obtained during the POCS were according to each center's standards.

Outcome measures

The primary end point for this study was procedural success, which for the indeterminate strictures or undefined filling defects was defined as: (i) the ability to visualize the stricture or defect (with image quality rated "excellent," "good," "fair," "poor," or "unable to visualize"); (ii) the ability to provide a visual impression of malignancy; and (iii) when applicable, the ability to obtain SpyBite biopsies that were adequate for histology.

Secondary end points included: (i) evaluation of serious adverse events related to the POCS procedure up to 72 hours post-procedure; (ii) impact of the SpyGlass procedure on the suspected diagnosis compared to a prior ERCP; (iii) evaluation of the impact of antibiotic use on the incidence of serious adverse events related to the device and/or procedure; (iv) for patients undergoing SpyBite biopsies, correlation between the number of biopsies and a conclusive histopathology diagnosis being obtained.

The direct visualization image features that were reported during the POCS included: the absence of any features; the presence of a growth, stricture, hyperplasia, ulceration, a mass, dilated tortuous vessels, papillary or villous projections, intraductal nodules; or the presence of mucus.

Statistical analysis

Summary statistics were used to analyze the results of this study. Specifically, categorical measures were analyzed using rates, and comparisons (e. g. image quality in two Spyglass systems) were performed using a Fisher's exact test. Confidence intervals (CI) were calculated using Clopper–Pearson exact methods. Continuous measures were analyzed using either mean and standard deviation (SD) or median and range, and comparisons were tested using a *t* test or Wilcoxon's rank sum test. Count variables (e. g. number of SpyBite biopsies) were analyzed using mean (SD) and were tested using a negative binomial model.

Univariate and multivariate analyses were performed to identify predictive factors for the primary end point of procedural success in the evaluation of indeterminate biliary strictures using POCS. The baseline variables included in the analysis were: age, sex, previous ERCP, previous cholangitis, acute pancreatitis in the last 4 weeks, prior cholecystectomy, chronic pancreatitis, liver cirrhosis, location, and whether the target lesion was located in the common bile duct. These were performed using logistic regression with a Firth penalized likelihood method. Multivariate model building was performed using stepwise model building procedures, with entry and exit significance level set a $P<0.1$.

Ad hoc analyses were performed to evaluate the associations between the accuracy of the visual impression of the endoscopist, as well as the histological diagnosis reached, when compared to the final 6-month diagnosis reached. These were performed using the same univariate and multivariate methods as described above, along with the same baseline variables.

All *P* values were two-sided, and all results were considered significant if the *P* value was <0.05. All analyses were performed in SAS version 9.4. The Sankey diagram was generated using R Studio [8] using the R statistical language [9] for data visualization [10].

Results

Patient and procedure characteristics

Between September 2014 and April 2016, 289 patients with indeterminate biliary strictures were evaluated with 290 procedures. The procedures were performed by the Legacy system

▶ **Table 1** Baseline characteristics of the 289 enrolled patients.

Characteristic	
Age, mean (SD), years	61.5 (13.8)
Male, n (%)	177 (61.2 %)
Medical and surgical history, n (%)	
▪ Cholangitis in last 4 weeks	68 (23.5 %)
▪ Acute pancreatitis in last 4 weeks	4 (1.4 %)
▪ Chronic pancreatitis	3 (1.0 %)
▪ Liver cirrhosis	9 (3.1 %)
▪ Prior cholecystectomy	30 (10.4 %)
▪ Prior liver transplantation *	1 (0.3 %)
▪ Previous ERCP	174 (60.2 %)

* This case was a living-donor liver transplantation.

▶ **Table 2** Lesion location, image quality, and biopsy procedural information.

	Legacy (n = 173 procedures)	DS (n = 117 procedures)	Overall (n = 290 procedures)	*P* value
Location of lesion, n (%)				0.72
▪ Common bile duct	84 (48.6 %)	54 (46.2 %)	138 (47.6 %)	
▪ Hilar region	31 (17.9 %)	18 (15.4 %)	49 (16.9 %)	
▪ Common hepatic duct	27 (15.6 %)	20 (17.1 %)	47 (16.2 %)	
▪ Left main hepatic duct	11 (6.4 %)	8 (6.8 %)	19 (6.6 %)	
▪ Right main hepatic duct	5 (2.9 %)	8 (6.8 %)	13 (4.5 %)	
▪ Diffuse/multiple locations	7 (4.0 %)	2 (1.7 %)	9 (3.1 %)	
▪ Intra-hepatic biliary ducts	4 (2.3 %)	4 (3.4 %)	8 (2.8 %)	
▪ Ampullary area	1 (0.6 %)	0 (0.0 %)	1 (0.3 %)	
▪ Gallbladder	1 (0.6 %)	0 (0.0 %)	1 (0.3 %)	
▪ Cystic duct	2 (1.2 %)	3 (2.6 %)	5 (1.7 %)	
Quality of SpyGlass image, n (%)				< 0.001
▪ Excellent	56 (32.4 %)	85 (72.6 %)	141 (48.6 %)	
▪ Good	76 (43.9 %)	27 (23.1 %)	103 (35.5 %)	
▪ Fair	37 (21.4 %)	4 (3.4 %)	41 (14.1 %)	
▪ Poor	3 (1.7 %)	0 (0.0 %)	3 (1.0 %)	
▪ Unable to visualize	1 (0.6 %)	1 (0.9 %)	2 (0.7 %)	
Biopsy performed, n (%)	121 (69.9 %)	89 (76.1 %)	210 (72.4 %)	0.29
▪ SpyBite biopsy taken, n (%)	102 (59.0 %)	80 (68.4 %)	182 (62.8 %)	0.11
▪ No. of SpyBite forceps used per procedure, mean (SD)	1.1 (0.5)	1.0 (0.2)	1.1 (0.4)	0.55
▪ No. of samples collected per procedure, mean (SD)	2.6 (1.4)	3.7 (2.0)	3.1 (1.8)	< 0.001
▪ Sample taken using SpyBite adequate for histology, n (%)	95 (93.1 %)	74 (92.5 %)	169 (92.9 %)	0.99

SD, standard deviation.

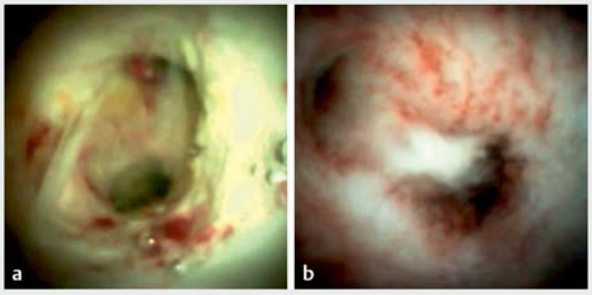
in 173 patients (58.9 %), and by the newer DS digital system in 116 patients (40.1 %). Baseline characteristics of the patients included in the analysis are provided in ▶ **Table 1**.

Cholangitis was reported in the 4 weeks preceding the POCS procedure in 23.5 % of patients and 1.4 % had an episode of acute pancreatitis. Liver cirrhosis was present in 3.1 % of the study cohort, and 1 % had a history of chronic pancreatitis. There was one patient who had undergone living-donor liver transplantation, and 10.4 % of the cohort had undergone a prior cholecystectomy. A sphincterotomy was performed in almost all patients, either at the time of the prior ERCP (which in some cases required extension) or at the time of the POCS. The majority of the lesions found were in the common bile duct (47.6 %), common hepatic duct (16.2 %), or hilar region (16.9 %), which represented 80.7 % of all the lesions evaluated (▶ **Table 2**).

Quality of SpyGlass image and diagnostic accuracy of POCS visualization

The image quality was described as excellent in 141/290 of the procedures (48.6 %), good in 103/290 (35.5 %), fair in 41/290 (14.1 %), and poor in 3/290 (1 %) (▶ **Table 2**). There were two procedures where the endoscopist was unable to visualize the bile duct adequately. The image quality of the DS system was described as excellent more frequently than that for the Legacy system (72.6 % vs. 32.4 %, respectively; $P < 0.001$).

The visual impression as to whether the stricture was malignant or benign (▶ **Fig. 1**) had a sensitivity of 86.7 %, specificity of 71.2 %, a positive predictive value (PPV) of 65.8 %, and a negative predictive value (NPV) of 89.4 % with an overall accuracy of 77.2 % (▶ **Table 3**). A total of 39 % of the patients were diagnosed to have malignancy by 6 months of follow-up.

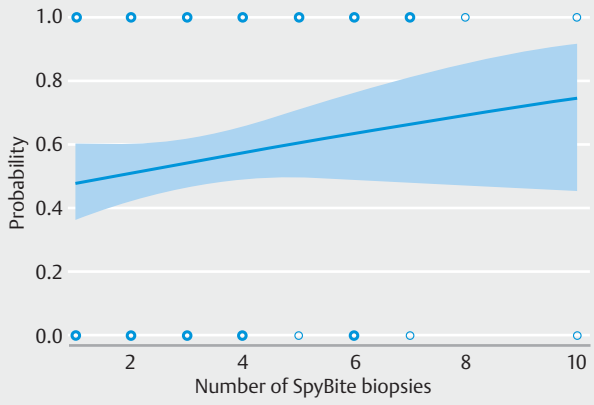


▶ **Fig. 1** Indeterminate biliary strictures identified using peroral cholangioscopy (POCS) as: **a** benign; **b** malignant.

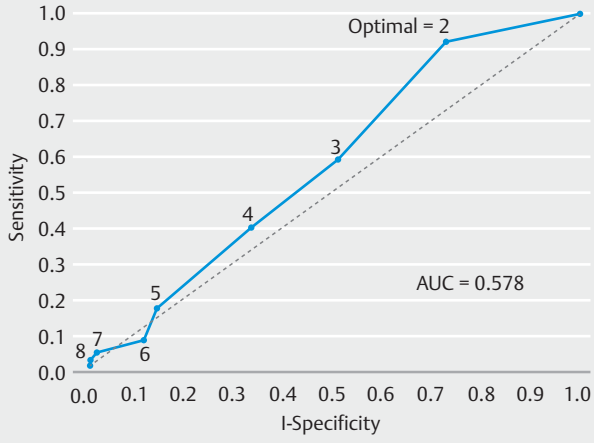
▶ **Table 3** Diagnostic accuracy based on peroral cholangioscopy (POCS) visualization or histopathology of malignancy compared to diagnosis at 6 months of follow-up.

	Diagnosis based on POCS visualization (95 %CI) (n = 290 procedures)	Diagnosis based on SpyBite histopathology (95 %CI) (n = 163 procedures)
Sensitivity	86.7 % (79.1 % – 92.4 %)	75.3 % (65.0 % – 83.8 %)
Specificity	71.2 % (63.9 % – 77.7 %)	100 % (95.1 % – 100 %)
Positive predictive value	65.8 % (57.6 % – 73.3 %)	100 % (94.6 % – 100 %)
Negative predictive value	89.4 % (83.1 % – 93.9 %)	77.1 % (67.4 % – 85.0 %)
Overall accuracy	77.2 % (72.0 % – 81.9 %)	86.5 % (80.3 % – 91.3 %)

CI, confidence interval.



▶ **Fig. 2** Predicted probability of making a diagnosis of malignancy as a function of the number of biopsies based on linear regression that showed no association ($P = 0.16$).



▶ **Fig. 3** Receiver operating characteristic (ROC) curve to estimate the optimal number of biopsies needed to make a diagnosis of malignancy in patients with indeterminate biliary strictures. AUC, area under the curve.

There was no difference in the diagnostic accuracy between the Legacy and DS systems when comparing the final diagnosis to the visual impression obtained during the procedure. Image quality and diagnostic accuracy of the visual impression did not vary significantly by location.

Histological sampling

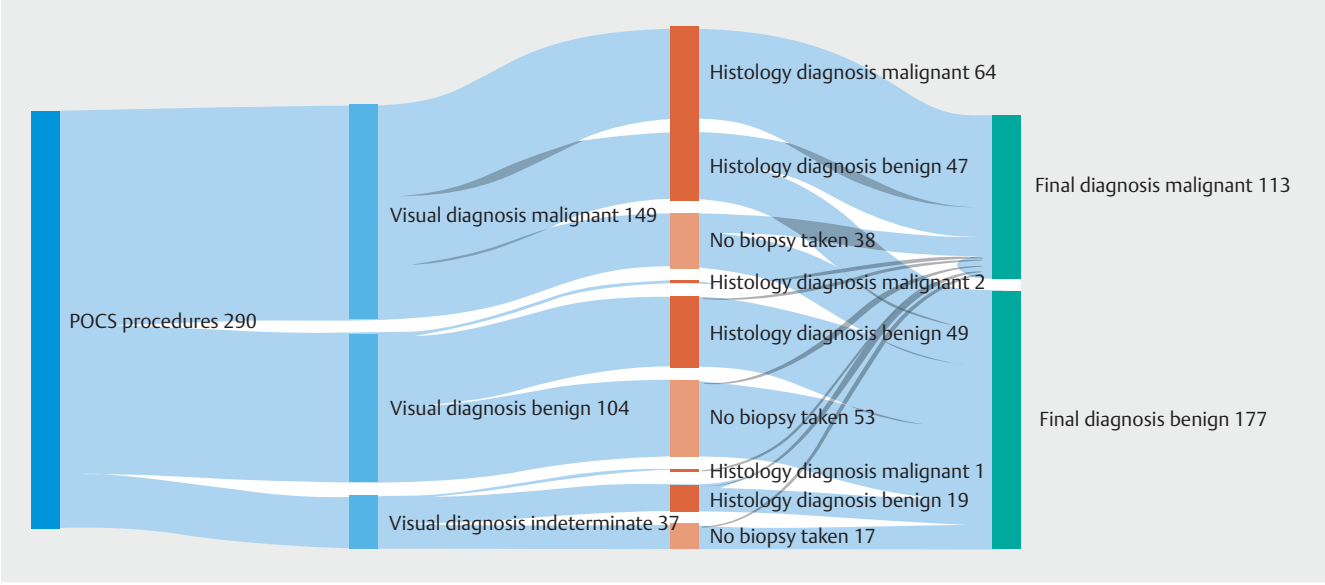
Biopsies were obtained in 210/290 of the procedures (72.4 %) with 182/290 (62.8 %) performed using the dedicated biopsy forceps (SpyBite) (▶ **Table 2**). On average, a single biopsy forceps was used per procedure (mean [SD], 1.1 [0.4]). There was a higher mean number of biopsies obtained in the DS cohort than with the Legacy group (3.7 biopsies vs. 2.6 biopsies; $P < 0.001$) but there was no difference in the adequacy in the samples obtained (92.5 % vs. 93.1 %; $P = 0.99$).

When compared to the final diagnosis after the 6-month follow-up period, the POCS-guided biopsy histology had a sensitivity of 75.3 %, specificity of 100 %, PPV of 100 %, NPV of 77.1 %, and an overall accuracy of 86.5 % (▶ **Table 3**).

There was no difference in the diagnostic accuracy of biopsies obtained by the Legacy system compared with the DS system. Additionally, there was no optimum number of biopsies where a histological diagnosis of malignancy was more probable in patients with indeterminate biliary strictures (▶ **Fig. 2**) as demonstrated by an area under the receiver operating characteristic (ROC) curve of 0.578 (▶ **Fig. 3**). The diagnostic accuracy of biopsy histopathology did not vary significantly by location.

Procedural success

The procedure was considered successful in visualizing the stricture/defect in 286/290 procedures (98.6 %) and in providing a visual impression as to whether the lesion appeared malignant or benign in 253/290 procedures (87.2 %). For the pro-



▶ **Fig. 4** A Sankey diagram depicting the patient flow throughout the duration of the study using diagnostic evaluation with peroral cholangioscopy (POCS).

cedures where a biopsy was obtained, 169/182 (92.9%) were deemed adequate for analysis. Therefore, the overall procedural success was 241/290 (83.1%; 95%CI 78.3%–87.2%).

Impact of the SpyGlass procedure on patient management

In this cohort, POCS influenced the management in 249/289 patients (86.2%; 95%CI 81.6%–89.9%) by determining the cause of the biliary stricture (50.9%) or the cause of an unexplained filling defect or biliary dilatation (37.4%), or by detecting stones missed by other evaluation methods (1.7%). The sequence of visual impression and histological diagnosis and the final diagnosis for the patients evaluated in the study is shown in ▶ **Fig. 4**.

A biliary stent was inserted in 29.4% of patients during the same ERCP procedure as the cholangioscopy. Surgery was avoided in 22.2% of patients, while 19.0% were referred to surgery and 5.19% were referred for combined chemoradiotherapy.

Adverse events

Five serious adverse events related to the POCS procedure occurred in this cohort (1.7%; 95%CI 0.5%–4.0%)). Three patients in the cohort developed cholangitis (1.0%), all of whom had received prophylactic antibiotics. There was a single patient with acute pancreatitis and a single patient with bleeding. There was no mortality related to the POCS procedures in this cohort of patients.

Multivariate analyses

On univariate analysis, the only factor associated with a higher odds of success was older age, with an odds ratio (OR) of 1.3 (95%CI 1.1–1.6) for each 10-year increment in age, which persisted on multivariate analysis (OR 1.4 [95%CI 1.1–1.7]).

None of the baseline variables included in the ad hoc analysis were associated, either on univariate or multivariate analysis, with the accuracy of the visual impression made during POCS; these included age, sex, previous ERCP, use of the newer DS system, previous cholangitis, acute pancreatitis in the last 4 weeks, prior cholecystectomy, chronic pancreatitis, liver cirrhosis, location, whether the target lesion was located in the common bile duct, and the number of biopsies obtained.

Discussion

Indeterminate biliary strictures pose a significant challenge to endoscopists and their patients. The primary aim is to differentiate benign from malignant pathology so as to guide appropriate therapy and avoid the morbidity, mortality, and healthcare costs associated with unnecessary treatment, in particular surgical intervention. Although the majority of indeterminate biliary strictures are neoplastic, approximately 30% are benign. A quarter of surgical resections for suspected neoplastic lesions ultimately confirm benign pathology [11]. Interestingly, in our cohort, the rate of malignant diagnosis was higher, which might represent a more aggressive evaluation strategy with a lower threshold for performing POCS at these referral centers.

Although ERCP is still considered the main diagnostic modality for tissue/cytology acquisition from biliary lesions, without the use of cholangioscopy, the diagnosis of biliary malignancy using brush cytology and intraductal biopsy suffers from limited sensitivity being 45% (95%CI 40%–50%) and 48.1% (95% CI 42.8%–53.4%), respectively [12]. Therefore, other diagnostic modalities are needed. The current study demonstrates that POCS can be performed with a high success rate for visualizing indeterminate strictures, in addition to facilitating a visual impression of benign versus malignant etiology. Also, POCS was

associated with an acceptable adverse event rate that was no higher than standard ERCP.

To ensure clinical relevance, the diagnostic performance of POCS must provide an improvement relative to the currently performed techniques. A Spanish study including 52 patients with indeterminate biliary strictures demonstrated that POCS had a sensitivity, specificity, and diagnostic accuracy of 88.5%, 80%, and 83%, respectively [13], while a SpyGlass DS subanalysis (n = 19, including 13 indeterminate bile duct strictures) found that the visual appearance had a sensitivity of 89%, specificity of 100%, a PPV of 100%, an NPV of 75%, and an overall diagnostic accuracy of 91%. In a meta-analysis by Navaneethan et al. [14], the visual appearance on POCS had a pooled sensitivity of 83.3% (95%CI 77.7% – 88%) and a specificity of 81.8% (95%CI 75.9% – 86.7%), while for the detection of cholangiocarcinoma the pooled sensitivity was 68.4% (95%CI 61.7% – 74.6%), specificity 97.2% (95%CI 93.9% – 99.0%), and the pooled diagnostic OR was 63.8 (95%CI 27.1 – 150.5). Our cohort demonstrated numbers similar to this meta-analysis, with a sensitivity of 86.7% and a specificity of 71.2%.

The definition of indeterminate biliary strictures in earlier studies included strictures with no evidence of a mass lesion on cross-sectional imaging and negative brushings and/or biopsies on evaluation [15]. Other studies have used ERCP findings of a bile duct stricture with nondiagnostic intraductal biliary brushings and/or biopsies, and/or nondiagnostic endoscopic ultrasound fine-needle aspiration cytology [16]. Some groups used imaging as a possible criterion in the presence of a strong suspicion of malignancy [12]. These might be stricter definitions compared with that used in this cohort as negative brushings were not a prerequisite and a number of patients had not had a prior ERCP. Nonetheless, there is no unified definition and the patients included in our cohort represent cases that would typically be encountered in clinical practice.

In a large, multicenter study from Japan, the visualization of the target lesion was lower in those with intrahepatic (80%) and distal lesions (86.7%) compared with hilar, proximal (both 100%), and mid-bile duct lesions (94.1%) [17]. In our cohort, the procedure was considered successful in visualizing the stricture/defect in 286/290 procedures (98.6%). In the study by Pons Beltran et al. [13], adequate samples were obtained in only 73% of cases. This is much lower than our results (92.9% of samples being adequate for histological analysis).

The most common complication reported with POCS is cholangitis, which occurs in 0% – 14% of procedures [18] and is often mild and treated with oral antibiotics. Reports of severe or fatal cholangitis are rare [19]. In our cohort, the cholangitis rate was only 1%; importantly, prophylactic antibiotics were administered to all three of these patients. Other centers have reported cholangitis rates as high as 10.6% despite the use of prophylactic antibiotics [20].

A major issue that limits the dissemination of a diagnostic test is the variability in its performance and reproducibility. This is true for POCS, as a 2014 study found the interobserver agreement between the initial findings and final diagnosis to be slight (Fleiss' kappa statistic 0.01 – 0.20) [21]. Also, the assessment of the diagnostic accuracy of visual assessment of the strictures could not be isolated from the pretest probability that the endoscopist had based on the clinical presentation and context of the test. Endoscopists reviewing POCS recordings when blinded from the patients' details would ideally mitigate this bias.

Although the generalizability of the results of this series could be challenged as a consequence of being performed in high volume centers, the American Society of Gastrointestinal Endoscopy (ASGE) considers POCS a level III procedure [22]; as such, it is reasonable that such a study be performed in tertiary care centers. A limitation of this study was that the processing and reporting of the biopsies obtained was not centralized, potentially resulting in interinstitutional variability. The potential impact of this was reduced by using the 6-month clinical end point or definitive histology provided by surgical resection. Another potential unmeasured confounder was the method of sedation, which was determined by the treating endoscopist and institution. In a study by Kalaitzakis et al. [23], patients receiving conscious sedation had successful procedures less frequently when compared with those undergoing general anesthesia (75% vs. 87%, respectively; $P = 0.04$).

We acknowledge strengths and limitations that affect the interpretation of results from this study. This is one of the largest, if not the largest, cohorts reported of patients evaluated by POCS. Its multinational, multi-unit, multi-endoscopist methodology confers great generalizability relative to other studies. The prospective nature of the registry also captures the impressions of the endoscopists and time stamps them through an electronic system prior to the results of the biopsy and the final diagnosis at 6 months. This helps avoid a number of biases that are associated with retrospective studies. In addition, we applied the gold standard criterion of a 6-month follow-up end point. This is the most common timeframe used in the literature, with some studies specifying 6 months [16, 17, 24], while others have ranged from 12 to 18 months [23, 25, 26], or in between [15].

With regard to limitations, the baseline patient characteristics were collected by patient self-report and may have been subject to recall bias. Data were not available for some items that might have been of interest to clinicians, for example the number of procedures performed with ultraslim scopes, the proportion of patients who had previous stents or ERCP with standard transpapillary biopsies, or past imaging or laboratory data that might have influenced their management. Also, the findings in our cohort might not be generalizable to other patient populations, such as those with primary sclerosing cholangitis, as demonstrated in a recent publication from the Netherlands [27, 28]. Additionally, five of the authors have received monetary or research support from the study sponsor.

In conclusion, this large, real-life, prospective registry demonstrates that POCS is an effective and safe intervention in guiding the management of patients with indeterminate biliary strictures.

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The data, analytic methods, and study materials for this study may be made available to other researchers in accordance with the Boston Scientific Data Sharing Policy (http://www.bostonscientific.com/en-US/data-sharing-requests.html).

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Competing interests

Dr. Benedict Devereaux is a member of the speakers' bureau of Boston Scientific Corporation. Joyce Peetermans, Pooja G. Goswamy, and Matthew Rousseau are employees of Boston Scientific Corporation, the sponsor of this registry. Dr. Takao Itoi is a consultant to Boston Scientific Corporation, Olympus Corporation, Fujifilm Corporation, and Gadelius Medical. The remaining authors declare that they have no conflict of interest.

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